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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/672,429

09/26/2003

Robert O. Dempcy

17682A-003650US

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7590

09/14/2006

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EXAMINER

AGRAWAL, RITESH

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/672,429

Applicant(s)

DEMPCY ET AL.

Examiner

Ritesh Agrawal

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 110-127 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 110-127 is/are rejected.
- 7) ☒ Claim(s) 116 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 September 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>09/26/03, 02/25/04, 3/14/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of $(\text{NH}_2)_2\text{BuPPAOH}$ for claim 118, the left-most structure for claim 121, and hybridization conditions for claim 124 in the response filed 07/05/06 is acknowledged. Applicant's amendments filed 09/26/03 and 07/05/06 are acknowledged and entered.

Applicant's arguments are found persuasive and, as such, the species election requirement, mailed 06/01/06, has been withdrawn.

Claims 110-127 are pending and examined.

Priority

It is brought to applicant's attention that, for the purpose of examination, priority has not been granted to the claimed prior application 09/054,830 filed 04/03/98 for the elected invention because the Office was not able to determine that elected invention was disclosed in the claimed application. Application 09/054,830 does not disclose nearest-neighbor methods for the calculation of melting temperatures or duplex stability. Priority is granted to the later filed application 09/724,959 filed 11/28/00. Prior art published after the filing date for application number 09/054,830 but before the filing date for 09/724,959 may have been cited in the Office action. Applicant is requested to provide evidence that the elected invention is indeed disclosed in the prior application if applicant wishes to contest the citation of intervening prior art.

Information Disclosure Statement

The Information Disclosure Statement filed March 14th, 2005 has been entered and considered.

The Information Disclosure Statement filed February 25th, 2004, has been entered and considered. All of the references contained within the IDS filed 09/26/03 can be found on the 02/25/04 IDS. Therefore this IDS has not been separately considered.

Initialed copies of the form PTO-1449 are enclosed with this action.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: The description on page 3 of the specification refers to Fig. 5 but the drawings filed on 09/26/03 do not include a fig. 5. Sheet 6 of 6 of the drawings is not numbered as fig. 5. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The specification is objected to because of the following:

The use of the trademarks VARIAN and GENBANK has been noted in this application. VARIAN can be found, for example, on page 63 of the specification while GENBANK can be found, for example, on page 89. They should be capitalized wherever they appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

- (1) if a machine or apparatus, its organization and operation;
- (2) if an article, its method of making;
- (3) if a chemical compound, its identity and use;
- (4) if a mixture, its ingredients;
- (5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract of the disclosure is objected to because it is drawn to modified oligonucleotides whereas the invention is drawn to methods for calculating the stability of a nucleic acid duplex. Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The elected invention is drawn to a method of determining duplex stability whereas the title is directed to modified oligonucleotides.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 110-123 and 125-127 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The following analysis of facts of this particular patent application follow the analysis suggested in the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility"¹. Note that the text of the Guidelines is italicized.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- The claimed invention "transforms" an article or physical object to a different state or thing.*
- The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.*

¹ Available at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/guidelines101_20051026.pdf

In the instant case, the claimed invention does not "transform" an article or physical object to a different state or thing. This does not preclude the subject matter from being patentable as,

physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that produces a useful, tangible and concrete result. In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is "useful, tangible and concrete." The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory. (Guidelines, p. 20)

The question is thus whether the final result achieved by the claimed invention satisfies all three criteria of being useful, and concrete, and tangible.

Furthermore, the useful, tangible, and concrete result must be recited in the claim itself, rather than addressed in specification.

"TANGIBLE RESULT" The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. The opposite meaning of "tangible" is "abstract."

The instant claims are drawn to computational means for calculating duplex stability. However, as claimed, the method does not produce a real world result. For example, at least one embodiment of the method as claimed may take entirely within the

confines of a computer or a human mind without any communication to the outside world. At present, the result of the computational method steps is a ranking of a measure of the stability of an oligonucleotide duplex. There are no claim steps for the manipulation of this measurement that produce a tangible result. Thus, at least one embodiment of the claimed invention does not produce a tangible result.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 110-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 110 and 111 recite the limitation "the N-1 neighboring base pairs" in lines 7-8. There is insufficient antecedent basis for this limitation in the claim. There is no prior reference to this term within claims 110 and 111.

Claim 113 is indefinite for the use of the term Genbank. Claims containing trademarks must use the term as a source of a product rather than the product itself (See MPEP 2173.05 (u)). In this case, the usage of the trademarked term GENBANK refers to the database product itself.

The term "superior" in claims 117, 126, and 127 is a relative term which renders the claim indefinite. The term "superior" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use

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of the term superior renders indefinite the extent of mismatch discrimination obtained with modified versus unmodified nucleotides.

Claim Objections

Claim 116 is objected to because of the following informalities:

The claim recites the phrase "said modified base a locked nucleic acid sugar."

There appears to be grammatical problems in need of correction. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

Claims 110-111, 114-115, 117, 123, and 126 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin et al. (Analytical Biochemistry, Vol. 260, pages 56-63, 1998).

Claims 110 and 111 are drawn to methods of calculating the duplex stability of an oligonucleotide with a modified base using a nearest-neighbor model. Claim 111 is

further drawn to specifically calculating duplex stability through the calculation of melting temperature.

Griffin et al. disclose a method for calculating the duplex stability and melting temperature of nucleic acids modified with PNA using nearest neighbor models (see abstract, lines 1-6 and 17-18).

Regarding claims 114 and 115, Griffin et al. disclose the use of PNA as the base modification (see cited text for claims 110-111).

Regarding claims 117 and 126, increased mismatch discrimination is a property of a PNA modified oligonucleotide molecule. The reference teaches calculating the stability of a PNA modified oligonucleotide (as cited above) but it doesn't specifically disclose that PNA modified nucleotides have greater mismatch discrimination. If the PNA modification provides for an oligonucleotide with increased mismatch discrimination and the reference teaches calculating the stability of an oligonucleotide with a PNA modification, then the reference is teaching the calculation of the stability of a molecule with superior mismatch discrimination whether or not it explicitly discloses that property (See MPEP 2112).

Regarding claim 123, Griffin et al. disclose that their average difference between calculated and measured duplexes was 2.2 degrees, reasonably about 2 degrees (page 59, 1st column, paragraph 5, lines 4-6).

Claims 110, and 125 are rejected under 35 U.S.C. 102(e) as being anticipated by Lizardi et al. (U.S. Patent # 6, 403, 319) with an effective filing date of August 13th, 1999.

The claims are drawn to a method for calculating the stability of a modified oligonucleotide that serves as a capture probe wherein the method uses nearest neighbor models.

Lizardi et al. disclose capture probes in the form of detector probes that are used to capture other nucleic acid molecules (column 10, lines 60-61). Lizardi et al. further disclose that these probes can contain modified nucleotides (column 11, lines 31-33). Lizardi et al. disclose that the duplex stability of these probes can be calculated using a variety of methods including those using nearest-neighbor models (column 12, lines 51-53, see the Santa Lucia reference cited therein).

Claims 110-113 and 118-122 rejected under 35 U.S.C. 102(e) as being anticipated by Lokhov et al. (US Publication #20030235822, December 25th, 2003) with a priority date of 11/28/00.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 110-111 are drawn to a method for predicting duplex stability.

Claim 1 of Lokhov et al. discloses a computer-implemented method of predicting the melting temperature, which is a measure of duplex stability.

With respect to claims 112-113, Lokhov et al. disclose a computer-implemented method of predicting the melting temperature where data is derived from GENBANK (claim 2).

With respect to claim 118, Lokhov et al. disclose a computer-implemented method for predicting a melting temperature from one of the named structures (claim 7).

With respect to claim 119, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature of an oligonucleotide with one of those minor groove binders (claim 24).

With respect to claim 120, Lokhov et al. disclose a computer-implemented method for predicting a melting temperature for an oligonucleotide with an attached minor groove binder (claim 8).

With respect to claim 121, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature for those different minor groove binders (claim 9).

With respect to claim 122, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature for an oligonucleotide where the minor groove binder is attached via a quencher molecule (claim 25).

Claims 110-113 and 118-122 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

In light of the reasons discussed below in the double patenting rejection, it is apparent that copending Application No. 10/176,972 contains claimed subject matter in claims 1-2, 7-9, and 24-25 that is not patentably distinct from that in the instant claims

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110-113 and 118-122. Because the inventive entity of the copending Application 10/176,972 is different from that of the instant application, a rejection under 35 U.S.C. 102(f) is appropriate. This rejection could be overcome by amendment of the appropriate claims so that the claimed subject matter is patentably distinct from that in the copending application, or by filing a declaration signed by the inventors of the rejected claimed subject matter (or by the assignee if the assignee is prosecuting the instant application under a 1.47 petition) stating that the inventive entity for the commonly claimed subject matter is identical.

Claims 110-111 are drawn to a method for predicting duplex stability.

Claim 1 of Lokhov et al. discloses a computer-implemented method of predicting the melting temperature, which is a measure of duplex stability.

With respect to claims 112-113, Lokhov et al. disclose a computer-implemented method of predicting the melting temperature where data is derived from GENBANK (claim 2).

With respect to claim 118, Lokhov et al. disclose a computer-implemented method for predicting a melting temperature from one of the named structures (claim 7).

With respect to claim 119, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature of an oligonucleotide with one of those minor groove binders (claim 24).

With respect to claim 120, Lokhov et al. disclose a computer-implemented method for predicting a melting temperature for an oligonucleotide with an attached minor groove binder (claim 8).

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With respect to claim 121, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature for those different minor groove binders (claim 9).

With respect to claim 122, Lokhov et al. disclose a computer-implemented method for predicting the melting temperature for an oligonucleotide where the minor groove binder is attached via a quencher molecule (claim 25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 110-114, 117-124, are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. (IDS, Biotechniques, Volume 27, pages 1218-1224, 1999) in view of Kutyavin et al. (Nucleic Acids Research, Volume 28, Number 2, pages 655-661, 2000).

The instant claims are drawn to a process of predicting the melting temperature of an oligonucleotide sequence by calculating the nearest neighbor thermodynamic parameters for each of the N-1 neighboring base pairs in the identified sequence, wherein the identified sequence includes at least one modified base.

Regarding claims 110 and 111, Schutz et al. teach a method for calculating T_m , that is implemented in a standard PC running Microsoft Windows and Excel (which would include a user interface) (page 1219, left column, Materials and Methods section). Schutz et al. discloses spreadsheet software (i.e. processing module that returns the T_m of the identified oligonucleotide sequence) for thermodynamic melting point prediction of oligonucleotide hybridization with and without mismatches (Abstract etc.). The method of Schutz et al. uses the nearest neighbor thermodynamic parameters wherein a single base pair binding is influenced by the surrounding base pairs (page 1218, right column, lines 8-30, and page 1219, left column, last paragraph).

However Schutz et al. do not specifically teach calculating the thermodynamic parameters for an identified sequence that includes a least one modified base.

Kutyavin et al. teach calculating the thermodynamic parameters for an identified sequence that includes at least one modified base (page 657, left column).

Schutz et al. describes an easy to use (page 1221, left column, Discussion section) thermodynamic melting point prediction program that can be used in almost every scientific laboratory that works with T_A-based molecular biological assays (page 1221, right column, third paragraph). In addition, Schutz et al. suggests that his method is applicable for choosing or designing probes that show the most discrimination (page 1221, right column, first full paragraph). Thus one of ordinary skill in the art at the time of the invention would have been motivated to use Schutz et al.'s method to determine the most discriminating probes for his experiments. Kutyavin et al. disclose the improved hybridization properties of their modified oligonucleotide probes (page 661, conclusion). Kutyavin et al. suggest that their probes are more sequence specific than standard DNA probes (abstract). In order to choose the most discriminating probes suggested by Kutyavin et al., one of ordinary skill in the art at the time of the invention would have been motivated to use Schutz et al.'s program with the method of Kutyavin et al. for making fluorogenic MGB probes having higher melting temperature and greater binding specificity. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the program described by Schutz et al. with the method of Kutyavin et al.

Regarding claims 112-113, Schutz et al. teach users can enter the sequence from the GENBANK database (page 1219, right column, lines 10-13).

Regarding claim 114, Kutyavin et al. disclose that the DP13 tripeptide can be attached to the ODN at either the C- or N-terminus (page 656, right column, Structure and Synthesis of 3'-MGB ODNs and DNA duplex section).

Regarding claim 117, Kutyavin et al. disclose that the modified oligonucleotide had superior mismatch discrimination (specificity) (abstract, lines 7-9 and 14-15).

Regarding claims 118, the method of Kutyavin et al. comprises PPA and PPG linkers (Figure 5).

Regarding claims 120-121, Kutyavin et al. disclose in Figure 5 a MGB with the formula of the first formula from the left of claim 121 wherein m is equal to 3, R^c is H, and R^d is an alkyl. It is noted that the formula of Kutyavin et al. has an alkyl with an OP03 at the 3' end that has been reasonably construed as a required substitution for said MGB to attach to an oligonucleotide.

Regarding claim 119, the oligonucleotide is Schutz et al. comprises an MGB, fluorescein (FAM), and TAMRA quencher (page 637, right column, lines 12-16).

Regarding claim 122, Kutyavin et al. disclose that the MGB is attached to the oligonucleotide via PPG TAMRA quencher molecule as described in Figure 5. It is noted that the "G*" indicates the linking position of the PPG TAMRA quencher molecule.

Regarding claim 123, Schutz et al. disclose that their algorithm predicts melting temperature with an accuracy of ± 2.4 degrees (about 2 degrees) (page 1223, 1st column, 1st paragraph, lines 11-13 and figure 4).

Regarding claim 124, Schutz et al. disclose that the method can calculate melting temperature for hybridization (page 1223, 2nd column, 1st paragraph, lines 1-3).

Claims 110-114, 116-117, 123-124, and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutz et al. (Biotechniques Volume 27, pages 1218-1224, 1999) in view of Singh et al. (IDS, Chem. Comm., 1998).

The instant claims are drawn to a process of predicting the melting temperature of an oligonucleotide sequence by calculating the nearest neighbor thermodynamic parameters for each of the N-I neighboring base pairs in the identified sequence, wherein the identified sequence includes at least one modified base.

Regarding claims 110 and 111, Schutz et al. teach a method for calculating T_m that is implemented in a standard PC running Microsoft Windows and Excel (which would include a user interface) (page 1219, left column, Materials and Methods section). Schutz et al. discloses spreadsheet software (i.e. processing module that returns the T_m of the identified oligonucleotide sequence) for thermodynamic melting point prediction of oligonucleotide hybridization with and without mismatches (Abstract etc.). The method of Schutz et al. uses the nearest neighbor thermodynamic parameters wherein a single base pair binding is influenced by the surrounding base pairs (page 1218, right column, lines 8-30, and page 1219, left column, last paragraph).

However Schutz et al. do not specifically teach calculating the thermodynamic parameters for an identified sequence that includes at least one modified base.

Singh et al. teach calculating the thermodynamic parameters for an identified sequence that includes a base modified as a locked nucleic acid (page 455, 2nd column, 2nd paragraph, lines 8-12).

Schutz et al. describes an easy to use (page 1221, left column, Discussion section) thermodynamic melting point prediction program that can be used in almost every scientific laboratory that works with T_a-based molecular biological assays (page 1221, right column, third paragraph). In addition, Schutz et al. suggests that his method is applicable for choosing or designing probes that show the most discrimination (page 1221, right column, first full paragraph). Thus one of ordinary skill in the art at the time of the invention would have been motivated to use Schutz et al.'s method to determine the most discriminating probes for his experiments. Singh et al. disclose increased stability and selectivity of modified oligonucleotide probes (page 455, abstract). Singh et al. suggest that their probes are more sequence specific than standard DNA probes (abstract; page 456, 1st column, 2nd paragraph, lines 9-11). In order to choose the most discriminating probes suggested by Singh et al., one of ordinary skill in the art at the time of the invention would have been motivated to use Schutz et al.'s program with the method of Singh et al. for making locked nucleic acid probes having higher melting temperature and greater binding specificity. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the program described by Schutz et al. with the method of Singh et al.

Regarding claims 112-113, Schutz et al. teach users can enter the sequence from the GenBank database (page 1219, right column, lines 10-13).

Regarding claim 114, Singh et al. disclose the use of a locked nucleic acid (abstract).

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Regarding claim 117, Singh et al. disclose that the modified oligonucleotide had superior mismatch discrimination (selectivity) (abstract).

Regarding claim 123, Schutz et al. disclose that their algorithm predicts melting temperature with an accuracy of +/- 2.4 degrees (about 2 degrees) (page 1223, 1st column, 1st paragraph, lines 11-13 and figure 4).

Regarding claim 124, Schutz et al. disclose that the method can calculate melting temperature for hybridization (page 1223, 2nd column, 1st paragraph, lines 1-3).

Regarding claim 127, Singh et al. disclose that the locked nucleic acid modification has increased mismatch discrimination (page 456, 1st column, 2nd paragraph, lines 9-11).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

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patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 110-113 and 118-122 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 6-9, and 24-25 of copending Application No. 10/176,972. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions are a variant of each other. For example, the claims of copending Application No. 10/176,972 specifically recite the limitations of "a computer implemented method", "A computer readable medium", or "system." However, claims 112 and 113 of the instant application, respectively, recite the limitation of "a database source" and "Genbank" which could reasonably be construed as computer implemented etc.

Further, one of ordinary skill in the art would have been motivated to examine the specification for the computer related limitations (page 87-89) disclosed in the instant application. "The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent." (MPEP § 804 (11) (B) (1))

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ritesh Agrawal whose telephone number is (571) 272-2906. The examiner can normally be reached on 8:30 AM - 5:00 PM M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ritesh Agrawal

RA  9/1/06